

REMARKS

Claims 13, 61-67, 70, and 76 are pending in this application. Claims 68, 71-73, 75, 77 and 79 have been withdrawn from consideration. No claim amendments are made in this paper, and thus, no new matter has been introduced.

Applicants appreciate the Examiner's withdrawal of the rejections under 35 U.S.C. § 112, second paragraph and under 35 U.S.C. § 102(e).

Applicants respectfully submit that the pending claims are allowable at least for the following reasons.

I. The Rejection Under 35 U.S.C. § 103(a) Should be Withdrawn.

In the Office Action, the rejections of claims 13, 61-67, 70 and 76 as being unpatentable over Morgan *et al.*, U.S. Patent No. 6,274,579 ("Morgan") in view of Gelenberg *et al.*, *Report on efficacy of treatments for bipolar disorder*, 29(4) *Psychopharmacol Bull.* 447, 447-56 (1993) ("Gelenberg") are maintained for reasons of record in the previous Office Action filed on March 5, 2008. Applicants respectfully transverse this rejection.

The current standard of obviousness takes into account (1) whether there would have been a "reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed invention does;" and (2) whether there would have been a reasonable expectation of success. (*See e.g., PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007) ("The burden falls on the patent challenger to show by clear and convincing evidence that a person of ordinary skill in the art would have had reason to attempt to make the composition or device, or carry out the claimed process, and would have had a reasonable expectation of success in doing so.") (internal quotations omitted)).

At the outset, Applicants respectfully reiterate that the claims are not obvious for at least the reasons set forth in the previous response of July 2, 2008, which is incorporated herein by reference. Specifically, Applicants respectfully submit that (1) there would have been no reason for a person skilled in the art to combine the teachings of the cited references, Morgan and Gelenberg, to arrive at the claimed method; and (2) the combined teachings of

cited references would not have provided the requisite expectation of success in the instant claims.

In response, it is alleged in the Office Action that Applicants' submission is unpersuasive, allegedly because Morgan discloses that "the activity [of bupropion] resides in the (S,S)-hydroxybupropion metabolite." (Office Action, page 3). Column 2, lines 16-20 of Morgan is referred to in connection with this allegation. (*Id.*).

In this regard, Applicants respectfully point out that the portion of Morgan referred to in the Office Action is interpreted by the Examiner out of context of what Morgan as a whole discloses. For example, Morgan clearly discloses that "Bupropion hydrochloride ... is marketed ... for the treatment of depression." (Morgan, col. 1, lines 15-18) (emphasis added). Upon this premise, Morgan teaches that "[w]hile the mechanism of action of bupropion, as with other antidepressants, is unknown, it is presumed that this action is mediated by noradrenergic and/or dopaminergic mechanisms." (*Id.*, col. 1, lines 24-27) (emphasis added). As can be seen from these passages, where bupropion's activity, or mechanism of such activity, is referred to in Morgan, particularly near the portion of Morgan to which the Examiner refers, the term "activity" appears to mean the "antidepressant" activity exhibited by bupropion. Consequently, Applicants respectfully submit that the allegation that those skilled in the art would have thought that (S,S)-hydroxybupropion may replace bupropion in any and all uses, based on Morgan's disclosure that "the activity" of bupropion resides in (S,S)-hydroxybupropion, is based on a misinterpretation of the term "activity" as used in the portions of Morgan referred to in the Office Action. In other words, Applicants respectfully submit that, while Morgan may have suggested to those skilled in the art that (S,S)-hydroxybupropion may replace bupropion in its use for the treatment of depression, or other specific disorders disclosed therein, Morgan would not have provided any suggestion or expectation regarding any disorders not specifically disclosed therein.

Further, in response to Applicant's previous submission, the Examiner, pointing to another portion of Morgan that states "behavioral and electrophysiological data suggest that the effects of [racemic bupropion] are mediated by a noradrenergic mechanism," asserts that the passage would have suggested that "(S,S)-hydroxybupropion is more potent for behavioral function than racemic bupropion, because (S,S)-hydroxybupropion ... is where the

activity reside for behavioral functions, such as mania and bipolar disorder.” (Office Action, page 3) (emphasis added). Applicants respectfully, but strongly, disagree with this allegation.

Applicants respectfully submit that the Examiner is improperly extrapolating the passage of Morgan referred to in the Office Action to cover any and all disorders related to behaviors. However, Applicants respectfully point out that the reference to “behavioral data” made in Morgan actually refers to a set of behavioral criteria designed to assess the antidepressant activity of a compound. In other words, what Morgan really provides is that, when a set of behavioral criteria was examined to assess the antidepressant activity of bupropion, it was reportedly found that the antidepressant effects of bupropion “are mediated by a noradrenergic mechanism.” For evidence, Applicants respectfully invite the Examiner’s attention to Cooper, *Neuropsychopharmacology* 11(2):133-41 (1994) (“Cooper”), the reference cited in Morgan to support the statement referred to the Office Action that “behavioral and electrophysiological data suggest that the effects of Wellbutrin [racemic bupropion] are mediated by a noradrenergic [NA inhibitor] mechanism.” (Office Action, page 3, citing Morgan, col. 7, lines 34-37). As the Examiner will see, the “behavioral experiments” provided in Cooper are directed to “[t]he antidepressant effects of bupropion ... determined with the Porsolt test.” (Cooper, page 135) (emphasis added). Thus, the data reported by Cooper does not teach or suggest that NA inhibitory effect is responsible for any disorders involving behavioral function. Therefore, while Cooper’s report may evidence that NA inhibitory effect is responsible for bupropion’s antidepressant activity, Cooper teaches or suggests nothing regarding the correlation of NA inhibitory effect and other disorders involving behavioral function.

Further, it is alleged in the Office Action that “although ‘the mechanism of action of bupropion, as with other antidepressants, is unknown,’ it does not mean that bupropion would not be used to treat anything.” (Office Action, page 4, citing Morgan, col. 1, lines 24-25). Applicants fully agree. Indeed, Morgan discloses the use of bupropion for specific disorders, a list of which does not encompass any of the disorders recited by the pending claims. However, Applicants respectfully points out that, by disclosing that “the mechanism of action of bupropion, ... is unknown,” Morgan would not have provided a sufficient reason to prompt a skilled person in the art to use bupropion to treat the disorders not specifically disclosed in it (*e.g.*, those recited in the claims) with a reasonable expectation of success,

much less to further replace bupropion with (S,S)-hydroxybupropion to arrive at the claimed methods.¹

In the Office Action, it is further alleged that because Gelenberg discloses that “‘bupropion may be better than other second-generation heterocyclic antidepressants,’ it does provide the desirability of singling out bupropion from a list of disclosed agents.” (Office Action, page 4). It is also alleged that Applicants fail to elaborate on how Gelenberg teaches away from using bupropion. (*Id.*).

In this regard, Applicants respectfully submit that Gelenberg discloses not only second-generation antidepressants such as bupropion, but also a number of other agents that have successfully treated acute bipolar depression, such as electroconvulsive therapy (“ECT”) (Gelenberg, page 447). In light of the successful examples disclosed by Gelenberg, one of ordinary skill in the art, upon reading the Gelenberg reference, would have focused on these better alternatives. Thus, it is respectfully pointed out that one would not have found a reason to single out a second-generation antidepressant, such as bupropion, in the first place. As well-known, existence of better alternatives is a mitigating factor for obviousness. (*See, e.g., Yamanouchi Pharmaceutical Co. Ltd. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1344-45 (selection of a compound for drug development that exhibited activity held to be not obvious in part because of known better alternatives²)).

Further, it is alleged in the Office Action that the ECT study cited in Gelenberg was not compared with a second-generation antidepressant and there were ECT biases in the study, as patients selected in this study had not responded satisfactorily to previous trials with antidepressants. (Office Action, page 5).

In this regard, Applicants respectfully submit that in addition to second-generation antidepressants, the ECT study cited in Gelenberg also exclude many other agents such as

¹ Further in this regard, Applicants respectfully point out that no basis is provided in the Office Action to support the allegation that “[i]n fact, bupropion is well known to be use for a variety of cerebral function ailments.”

² Even assuming, *arguendo*, that Gelenberg teaches bupropion is a better second-generation antidepressant, the Office Action does not explain why such a teaching would have motivated one skilled in the art to single out (S,S)-hydroxybupropion over the other disclosed agents, which are not limited to “second-generation antidepressants.”

lithium and valproate that are disclosed in Gelenberg. Thus, the allegation that the ECT study cited in Gelenberg was not compared with a second-generation antidepressant would not have been a sufficient reason to prompt a skilled person in the art to use bupropion, much less (S,S)-hydroxybupropion, in the treatment of bipolar depression. In other words, because the ECT study does not provide any data as to the use of a second-generation depressant, there would not have been any reason for a skilled person to single out a second-generation antidepressant, and then, single out bupropion, to use it in the methods recited by the instant claims. Further, the mere statement that many of the patients in the ECT study had not responded satisfactorily to previous trials with antidepressants does not indicate that patients who had responded well to antidepressants were intentionally excluded from the study. In fact, one of ordinary skill in the art, upon reading this statement and the ECT study, would have regarded ECT as a better alternative to other agents, such as a second-generation antidepressant (*e.g.*, bupropion), to treat bipolar disorder.³ Accordingly, there would not have been any reason for one of ordinary skill in the art to try a second-generation antidepressant, such as bupropion, to arrive at the methods recited by the pending claims.

Finally, Applicants respectfully submit that even assuming, *arguendo*, that Gelenberg somehow would have directed those skilled in the art to bupropion for the treatment of bipolar disorder, there still would have been no motivation to replace bupropion with (S,S)-hydroxybupropion to arrive at the claimed methods for the reasons discussed above in connection with Morgan.

II. Conclusion

For at least the foregoing reasons, Applicants respectfully submit that all of the pending claims are allowable, and respectfully request that the rejections be withdrawn.

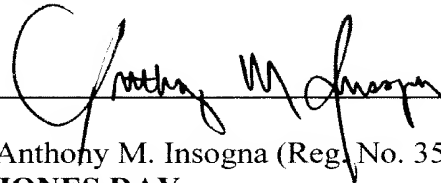
³ Further in this regard, it should be noted that Gelenberg discusses second-generation antidepressants in connection with “bipolar patients with depression.” (Gelenberg, page 451). Thus, it is unclear that the second-generation antidepressants are employed as treatment for depression as a symptom of bipolar disorder, or as treatment for bipolar disorder itself. As well-settled, case law is clear in that patentability of claims to the treatment of a disorder is not negated by prior disclosure of the treatment of the symptoms associated with the disorder. (*See, e.g., Rapoport v. Dement*, 254 F.3d 1053, 1060-1061 (Fed. Cir. 2001) (holding that claims to the treatment of sleep apneas using a compound were not anticipated by or obvious over prior art disclosure of the treatment of symptoms associated with sleep apnea using the same compound, because the reference’s mention of the possibility of administering the compound to patients suffering from sleep apnea was “for the purpose of treating [a symptom] in such patients, not for the purpose of treating the sleep apnea disorder itself.”)).

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A fee of \$540 is believed due for filing the Notice of Appeal. Please charge this and any other required fees for this submission or to avoid abandonment of the application to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

Date January 9, 2009

A handwritten signature in black ink, appearing to read "Anthony M. Insogna", is written over a horizontal line.

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